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1 **On hepatocellular carcinoma in South America and early-age onset of**  
2 **the disease**

3

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14

15 **Summary**

16 Hepatocellular carcinoma (HCC) is one of the most predominant tumor types  
17 worldwide, being particularly prevalent in sub-Saharan Africa and East Asia.  
18 However, HCC is inexplicably underreported in South America, despite  
19 unsettling clinical epidemiological trends of the disease on this continent.  
20 Here, we review the current knowledge on HCC presentation in Peru. We  
21 emphasize the well documented occurrence of an early-age nosological form  
22 of the disease in Andean descent populations. We further discuss the reasons  
23 for such clinical presentation, as well as the implications for liver cancer  
24 screening, management, and prevention.

25

26 **Keywords**

27 Liver cancer; Cancer risk factor; Hepatitis B virus (HBV); Indigenous people;  
28 Low- and middle-income countries; Global health transition

29

30 **Abbreviations**

31 AFP, alpha-fetoprotein; CELAC, Community of Latin American and Caribbean  
32 States; HBV, Hepatitis B virus; HBsAg, HBV surface antigen; HCC,  
33 Hepatocellular carcinoma; HCV, Hepatitis C virus; INEN, National Cancer  
34 Institute of Peru

35

36 **Introduction**

37 Hepatocellular carcinoma (HCC), the main form of primary liver cancer, is the  
38 seventh most common malignancy in incidence and the third leading cause of  
39 tumor-related death in the world [1]. Global clinical epidemiology of HCC  
40 reported hitherto chiefly delineates a prominent patient profile corresponding  
41 grossly to males over 45 years old with chronic liver diseases [2]. The  
42 incidence rate of HCC has doubled worldwide during the last two decades,  
43 with nearly 85% of the recorded cases and highest rates of disability-adjusted  
44 life-years occurring in low- and middle-income countries [3–5]. The largest  
45 burdens of HCC are borne in sub-Saharan Africa and East Asia, where the  
46 highly endemic chronic infection with hepatitis B virus (HBV) and dietary  
47 exposure to mutagenic aflatoxins potentialize one another [6,7]. In contrast,  
48 the incidence of HCC observed in more economically developed countries is  
49 associated most of all with hepatitis C virus (HCV) infection and heavy alcohol  
50 intake that are often associated with comorbid conditions, such as non-  
51 alcoholic fatty liver disease, diabetes mellitus, hereditary hemochromatosis or  
52 even  $\alpha$ -1 antitrypsin deficiency [6,8–10]. These risk factors trigger overtime  
53 liver cirrhosis that progresses in a significant proportion of cases in a hepato-  
54 carcinogenic process.

55

56 Reviews of the global burden of liver cancer have repetitively overlooked the  
57 epidemiology of the disease in South America creating a gap between the  
58 existing situation in the field and the overall clinical epidemiology of HCC  
59 described in the relevant literature [2,11]. Yet, while the incidence rate of  
60 primary liver cancer in South America is considered low to intermediate, the

61 epidemiological trends and the clinical presentation of HCC on this continent  
62 are displaying striking and worrying features as a whole. For example, South  
63 America is part of the Community of Latin American and Caribbean States  
64 (CELAC), which is the world region with the greatest incidence rise for liver  
65 cancer monitored during the last decade [12]. Furthermore, some physicians  
66 have reported on the continent, since the seventies, the dual occurrence of an  
67 early-onset form of HCC in younger individuals concomitantly with a more  
68 conventional older patient population.

69

#### 70 **Clinical epidemiological peculiarities and historical background**

71 In the first instance, Donayre and colleagues reported in a cohort of 60  
72 Peruvian HCC patients between 1969 and 1997 a mean age of 45 years old,  
73 with as many individuals in their third decade as people in their seventh  
74 decade [13]. The gender ratio (Male:Female) was balanced at 1.3, which  
75 appears to be another peculiarity of the clinical epidemiology of HCC in South  
76 America compared with elsewhere where the disease afflicts significantly  
77 many more men than women [14]. Forty-five percent of the patients were  
78 seropositive for the HBV surface antigen (HBsAg). Unfortunately, no formal  
79 diagnosis of cirrhosis was provided in this study. However, the authors  
80 consistently described an extensive hepatomegaly due to the explosive  
81 development of HCC in a short timescale as the predominant feature of  
82 clinical presentation.

83

84 Second, our group of medical practitioners and researchers described the  
85 clinical and demographic features of 232 consecutive patients who underwent

86 liver resection for HCC between 1990 and 2006 at the National Cancer  
87 Institute of Peru (INEN) [15]. In this cohort, the data were consistent with the  
88 observations made previously by Donayre and colleagues: the gender ratio  
89 was 1.5 and the mean and median ages were relatively young with 41.4 and  
90 36 years old, respectively. Forty-four percent of the patients were HBsAg  
91 seropositive [HBsAg(+)], and individuals presented with an extended  
92 hepatomegaly due to the development of sizeable HCC of 15 cm-diameter on  
93 average. Surprisingly, only 16.3% of the patients had cirrhosis, and the serum  
94 level of alpha-fetoprotein (AFP) was exceedingly high with a mean value over  
95 100,000 ng/mL.

96

97 Building on these studies, and in order to provide further insight into this  
98 intriguing clinical epidemiological situation, we assembled the largest cohort to  
99 date in South America; 1,541 Peruvian patients who were consecutively  
100 diagnosed with HCC at INEN between 1997 and 2010 [16]. A comprehensive  
101 analysis of the demographics substantiated that both mean and median ages  
102 observed were misleading and resulted, in fact, from a genuine bimodal  
103 Gaussian age-based distribution with a first peak at age 25 and a second  
104 peak at age 64, each mode integrating 50% of the overall patient population  
105 (Bimodality Index: 1.95; Moment of Mixture: 44.8 years old; Skewness  
106 Coefficients: +0.4 and -0.6, respectively).

107

108 This age-based dispersion delineated two distinct subpopulations of HCC  
109 patients with specific clinical features in terms of, *inter alia*, gender balance,  
110 tumor size, distant metastasis and recurrence [16]. For example, 71% of the

111 younger patient individuals were HBsAg(+) compared with 22.5% in the older  
112 patient population. As mentioned above, two remarkable hallmarks of HCC  
113 clinical presentation in Peru were the significant sizing of an intrahepatic  
114 tumor and the overall low frequency of associated cirrhosis in only 10% of the  
115 cases examined, this ratio barely reaching 5% in the younger patient  
116 population. Noticeably, AFP serum concentration was dramatically heightened  
117 in the younger patient group compared with the older one, culminating with c.  
118 380,000 ng/mL on average. Taken together, these findings support the idea  
119 that a singular biological process is driving liver tumorigenesis in a fraction of  
120 HCC patients in South America; and the clinical context described herein is  
121 uniquely concerning enough to be an important research topic.

122

123 Afterward, investigators originating from a broad consortium of regional  
124 countries have recently conducted a multicenter study in six South American  
125 countries including Argentina, Brazil, Colombia, Ecuador, Peru, and Uruguay.  
126 In two different articles analyzing the dataset collected from 1,336 patients  
127 with HCC between 2005 and 2015, they corroborated at an upper regional  
128 level the peculiarities of the disease originally observed in the Peruvian HCC  
129 patient population; unfortunately, though, they did not refer to the works  
130 previously published on this specific issue [17,18]. In their studies, the authors  
131 highlighted the large proportion of HCC diagnosed below age 50 in South  
132 America, notably in Peru, and correlated here again the occurrence of early  
133 age HCC with a high prevalence of HBV and mild pervasiveness of  
134 associated cirrhosis. In a subsequent scientific correspondence, Debes  
135 suggested environmental toxins as a foe on early-age HCC in South America,

136 pointing out the putative role of dietary aflatoxin exposure as already  
137 described in Africa [19,20].

138

### 139 **Mutation spectrum**

140 For our part, we undertook in a second phase a molecular analysis of nine  
141 HCC-related gene mutation hotspots (*i.e.*, *ARID2*, *AXIN1*, *BRAF*, *CTNNB1*,  
142 *NFE2L2*, *H/K/N-RAS*, and *TP53*) in 80 Peruvian HCC patients in furtherance  
143 to deepen our understanding of HCC in South America [21]. We  
144 demonstrated therein that Peruvian HCC featured a peculiar pattern of  
145 somatic mutations. The number of genetic alterations observed within these  
146 mutational hotspots was relatively low (0 to 3 per tumor) and the intensity of  
147 the mutagenic process rather mild with only two mutation hotspots (*i.e.*,  
148 *CTNNB1* and *TP53*) reaching 22% of mutants in both early- and late-onset  
149 forms of HCC. The preeminent class of HCC-associated genetic defects was  
150 epitomized by short deletions affecting notably the Wnt pathway. To the best  
151 of our knowledge, this mutation spectrum is not only unprecedented for HCC  
152 but also unique among solid tumors in which indels are usually monitored as a  
153 marginal subset of genetic alterations, confirming further the distinctive  
154 positioning of HCC in South America [22].

155

### 156 **Risk factors**

157 In the same study mentioned above from 2014, we addressed the  
158 commentary made *a posteriori* first by Chan and colleagues in 2017 and then  
159 by Debes in 2018 on the putative brunt of dietary aflatoxin intoxication in  
160 early-age onset of HCC afflicting the patients in South America [17,20].



161 Among the 80 Peruvian patients analyzed, we found only one carrier of the  
162 aflatoxin B1-induced R249S *TP53* gene mutation, who was, for the record, an  
163 older individual [21,23]. Together with the evaluation of the dietary aflatoxin  
164 risk factor, we also considered the possibility of a traditional misapplication of  
165 medicinal plants that could contribute to the development of early-age onset  
166 of HCC. Indeed, such self-medication disuse that enhances the risk of cancer  
167 has been highlighted for *Aristolochia* plants in Chinese traditional medicine  
168 [24]. We thus performed a cross-sectional study among 88 Peruvian patients  
169 with liver cancer to document their herbal medicine practices [25]. Most of the  
170 plant species cited in the survey were of common use in Peru, not being  
171 reported hitherto to have carcinogenic potential. Moreover, we discarded, in  
172 another preliminary report, the possibility in Peruvian HCC patients of chronic  
173 infection with the liver fluke *Fasciola hepatica*, which is found to be endemic in  
174 the Andean highlands and has previously been associated with liver  
175 parenchymal insults [26,27].

176

## 177 **Histology**

178 Taking into account that a significant fraction of HCC patients from South  
179 America do not present with full-fledged cirrhosis, we then decided to  
180 comprehensively specify, from a histological point of view, the pathological  
181 features of both tumor and non-tumor liver parenchymata of 50 HCC patients  
182 from Peru [28]. Interestingly, younger HCC patients presented with virtually no  
183 fibrolamellar carcinomas, which is a histotype occurring almost exclusively in  
184 non-cirrhotic liver and allegedly earlier than age 40 [29]. In addition, a large  
185 share of the liver tumors was steato-hepatitic HCC, a relatively rare variant

186 that is ordinarily associated with non-alcoholic fatty liver diseases and HCV-  
187 related cirrhosis [30]. Above all, our survey emphasized the relatively healthy  
188 status of the liver in Peruvian HCC patients. Tumors were arising mostly in  
189 liver parenchyma with low to mild degrees of fibrosis; this figure is at odds  
190 with the current view on the topic, as HCC in non-cirrhotic, non-fibrotic livers is  
191 claimed to represent a small minority of the cases [31]. Similarly, the levels of  
192 fatty liver and steatohepatitis (8%), as well as siderosis, were relatively low;  
193 this latter observation refuting one of the hypotheses formulated by Ponzetto  
194 and colleagues to explain the occurrence of early-age HCC among patients in  
195 South America [19]. In addition, the micro-steatotic pattern observed in case  
196 of infection with the genotype III of hepatitis Delta virus was conspicuously  
197 absent from the series. However, a significant proportion of younger HCC  
198 patients presented with a high density of clear cell foci of cellular alteration  
199 within the non-tumor liver parenchyma [28]. From a morpho-histological  
200 perspective, these hepatic foci are reminiscent of liver lesions observed in  
201 rodent models that have been subjected to genotoxic chemicals [32]. The  
202 exact burden of these clear cell foci and their potential role in liver  
203 carcinogenesis has to be ascertained in HCC patients from South America.  
204 Therefore, together with prevalent HBV infection, it is likely that the  
205 intercession of hitherto poorly documented environmental, metabolic, or  
206 infectious cofactors, such as alternative mycotoxins to aflatoxin B1, diabetes  
207 mellitus, or even co-infection with *Helicobacter* spp., which is highly endemic  
208 in the region [8,19,20,33].

209

210 **Role of hepatitis B virus**

211 As HBV is still suspected to be the prominent etiological agent and its  
212 prevalence monitored serologically associates with younger HCC patients in  
213 South America, we performed an in-depth molecular study of HBV infection in  
214 65 HCC patients from Peru [34]. A narrow majority of individuals (51%) were  
215 monitored HBsAg(+) and, thus, considered as genuinely infected at the onset  
216 of the disease. Using an ultra-sensitive assay, HBV DNA was, however,  
217 detected at a very low viral DNA burden in more than 80% of cases,  
218 disclosing hence a substantial rate of occult HBV infections in HCC patients  
219 [28,34,35]. A phylogenetic analysis of the viral sequences clustered every  
220 isolate within the sub-genotype F1b, which is a clade encountered historically  
221 in indigenous people of the Americas, notably in Alaska where the occurrence  
222 of early-age HCC has been described as well [36–38]. Intriguingly, HBV DNA  
223 sequence variations suggest an age-dependent restriction process, as viral  
224 genomes in younger patients displayed significantly higher frequency of  
225 mutations at di-pyrimidine sites (*i.e.*, TpT and CpC), which was until that time  
226 an unprecedented feature in the HBV genome [34]. These findings sharply  
227 contrast with the prevailing paradigm that relates higher HBV DNA loads with  
228 early-age HCC development [39]. We made assumptions that, in Native  
229 communities of the Americas, HBV-associated hepato-carcinogenesis might  
230 depart substantially from that broadly observed in other populations [34].

231

### 232 **Clinical management**

233 Altogether, the clinical and biological singularities of HCC and associated  
234 comorbidities observed in South America have some implications for the  
235 management strategies for screening, detection, diagnosis, and prognosis of

236 HCC patients from the region, as well as the vigilance of the population at  
237 risk. For instance, protocols used to screen for HBV infection, notably occult  
238 ones, as well as to detect early HCC development in subjects at risk should  
239 be tailored to the local situation. Furthermore, Trevisani and colleagues  
240 asserted that non-cirrhotic, non-fibrotic HCC clinically represents a distinctive  
241 nosological form of HCC with good amenability to liver resection even in  
242 cases of major hepatectomy [31]. This observation was confirmed by our  
243 review of the 253 Peruvian HCC patients who consecutively underwent a  
244 curative hepatectomy at INEN between 1991 and 2011 [40]. In our hands, the  
245 survival outcomes of liver resection observed were in good standing with  
246 those recorded with liver transplantation in cirrhotic patients with an early-  
247 stage tumor, despite the fact that the greatest part of the interventions  
248 performed were major hepatectomies due to the size and topography of the  
249 tumors exsected. This should be of great concern to the health policy-makers  
250 and group of experts aiming to build a regional consensus for HCC prognosis  
251 stratification and treatment guidelines and provide state-of-the-art  
252 prescriptions for local physicians and scientists, such as the Latin American  
253 Association for the Study of the Liver (LAASL) [41].

254

### 255 **Concluding remark**

256 Finally, another uncertainty concerns the magnitude of the phenomenon  
257 frequently observed in Peru; as to whether it is restricted to the Peruvian  
258 Andean communities or also occurs in other human populations, perhaps to a  
259 lesser degree. The observations made by Debes and colleagues confirm our  
260 original findings at an upper South American continental level [17,18].

261 Nevertheless, the occurrence of early-age forms of HCC in Alaskan Native  
262 people, 10,000 km distant from the indigenous communities of Peru but  
263 infected with the very same HBV clade, leads to speculation about the  
264 eventuality of a widespread, particular hepato-carcinogenic process shared  
265 among all populations with Americas' indigenous ancestry component  
266 [16,34,37,42].

267

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269 interest.

270

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278

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